UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,467	03/29/2004	Bill J. Peck	10031551-1	4799

22878 7590 02/11/2008

AGILENT TECHNOLOGIES INC.
INTELLECTUAL PROPERTY ADMINISTRATION,LEGAL DEPT.
MS BLDG. E P.O. BOX 7599
LOVELAND, CO 80537

EXAMINER	
CROW, ROBERT THOMAS	
ART UNIT	**PAPER NUMBER**
1634	

NOTIFICATION DATE	DELIVERY MODE
02/11/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPOPS.LEGAL@agilent.com

Office Action Summary	Application No.	Applicant(s)	
	10/813,467	PECK ET AL.	
	Examiner	Art Unit	
	Robert T. Crow	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-59 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-59 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2 November 2007 has been entered.

Status of the Claims

2. This action is in response to papers filed 2 November 2007 in which the 2 November 2007 claims 28 and 56 were amended, no claims were canceled, and no new claims were added. All of the amendments have been thoroughly reviewed and entered.

The previous rejections under 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

Claims 28-59 and 61 are under prosecution.

Terminal Disclaimer

3. As noted in the previous Office Action file 23 July 2007, the terminal disclaimer filed on 9 July 2007 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of Application Numbers 11/234,701, 10/813,337, 10/813,331, and 10/449,838 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 28-36, 38-44, 46-48, 50-52, 54-59, and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993) in view of Schleifer (A) (U.S. Patent No. 6,077,674, issued 20 June 2000) or Schleifer (B) (U.S. Patent No. 6,309,828, issued 30 October 2001).

Regarding claim 28, Anderson et al teach a method for producing an array of oligonucleotides on a substrate. In a single exemplary embodiment, Anderson et al teach locations having functional groups in the form of cpg supports having the first monomer attached (column 19, lines 55-58). Anderson et al also teach a first nucleotide capped with a trityl group attached to the surface of each support (i.e., substrate; column 19, line 40-column 20, line 50), followed by detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al teach displacing the deblocking fluid with a purging fluid; namely, the solid

supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20).

While the reference does not use the term "array", the term is defined by the website dictionary.reference.com as "a larger group, number or quantity of people or things".

In addition, while page 6 of the instant specification states that an array "includes any one-dimensional, two-dimensional or substantially two-dimensional (as well as a three-dimensional) arrangement of addressable regions bearing a particular chemical moiety or moieties," the specification yields no limiting definition requiring the regions of the array to be addressable.

Anderson et al teach production of a plurality of oligonucleotides attached to cpg substrate ("1. Oligonucleotide Synthesis", columns 19-22 and column 24, lines 5-35). Anderson et al further teaches the method wherein the polymers are cleaved from the support for subsequent use and/or immobilization (column 14 and column 20, liens 10-25); namely, hybridization to oligonucleotides immobilized on solid supports (column 20, lines 20-21). The clearly suggests that the polymers are subsequently immobilized.

Anderson et al does not specifically teach production of an addressable array, or that the oligonucleotides are covalently bonded at the plurality of addressable features.

However, polymer synthesis on cpg supports followed by polymer cleavage for production of an addressable array of covalently attached oligonucleotides was well known and routinely practiced in the art at the time the claimed invention was made as taught by Schleifer (A) and (B).

Schleifer (A) teaches a similar method of polymer synthesis comprising repeated monomer additions to cpg supports (column 9, lines 6-10), cleavage of the polymers from the supports (column 10, lines 10-15) and immobilization of the polymers to feature locations on the array (column 10, lines 37-42) whereby "costly and time consuming purification step" is avoided while providing a high purity full-

length oligonucleotide array (column 10, lines 47-51). Schleifer (A) also teach the full length (is synthesized and cleaved) oligonucleotides are linked to the array via conventional methods of attachment to a substrate (column 10, lines 36-42), wherein the linking agent provides a covalent bond between the oligonucleotide and the substrate surface (column 10, line 65-column 11, line 35). Thus, Schleifer (A) teaches the known technique of covalently linking oligonucleotides to a substrate at a plurality of addressable features (i.e., feature locations).

Schleifer (B) also teaches a similar method of polymer synthesis comprising repeated monomer additions to cpg supports, cleavage of the polymers from the supports and immobilization of the polymers to feature locations on the array (column 9, lines 22-column 10, line 30 and Example 3) whereby an addressable array is produced (see definition of array, column 1, lines 13-15). Schleifer (B) also teaches the deposition of the molecules onto the substrate utilizes covalent coupling of activated oligonucleotides with solid supports (column 9, lines 1-20). Schleifer (B) teaches this polymer synthesis coupled to array production is an efficient, cost-effective method of spatially integrating polymer synthesis and replicate array fabrication (Abstract, column 2, lines 22-31). Thus, Schleifer (B) teaches the known technique of covalently linking oligonucleotides to a substrate at a plurality of addressable features.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the polymers synthesized by Anderson et al to the further step of addressable array fabrication taught by Schleifer (A) and/or (B) to produce an addressable array comprising oligonucleotides covalently bound to the substrate at the plurality of addressable features. One of ordinary skill in the art would have been motivated to do so based on the well known practice of addressable immobilization of pre-synthesized polymers as taught by Schleifer (A) and (B). One of ordinary skill would have been further motivated to do so for the expected benefits of producing replicate arrays via efficient, cost-effective methods of spatially integrating polymer synthesis and array fabrication (Schleifer (B); Abstract, column 2, lines 22-31) and for the further benefits of providing high

purity full-length oligonucleotides while avoiding "costly and time consuming purification step" (Schleifer (A): column 10, lines 47-51).

Alternatively, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the displacement fluid synthesis steps of Anderson et al to the polymer synthesis of either Schleifer (A) or (B). Anderson et al teaches polymer synthesis in particulate beds is problematic in that fluid flow thorough the bed is non-uniform resulting non-uniform reactions and hence inefficient and inaccurate polymer synthesis (columns 1-4). Anderson et al further teach that their method of precise fluid control through the particle bed minimizes the problems of micro and macro-anomalous flow provides precise and efficient polymer synthesis (column 5-6). Therefore, one of ordinary skill in the art would have been motivated to apply the precisely controlled fluid flow of Anderson et al to the particle bed synthesis of Schleifer (A) and/or (B) for the expected benefit of precise and efficient polymer synthesis while eliminating the problems inherent in particle bed synthesis as taught by Anderson (columns 1-6).

In addition, it would have been obvious to the ordinary artisan that the known technique of using the polymer cleavage for production of an addressable array of covalently attached oligonucleotides as taught by Schleifer (A) and (B) could have been applied to the method of Anderson with predictable results because the polymer cleavage for production of an addressable array of covalently attached oligonucleotides as taught by Schleifer (A) and (B) predictably result in production of stable addressable array of oligonucleotides.

Regarding claim 29, the method of claim 28 is discussed above. Anderson et al also teach a blocked nucleoside monomer is attached to the substrate by contacting the substrate with a fluid comprising a blocked nucleoside monomer at a location on the substrate that comprises hydroxy groups; namely, the blocked monomer in step ii of Table I is added to the unblocked attached nucleotide of step i, which has a free hydroxyl group at the 5′ end generated by the detritylation step (column 19, line 40-column 20, line 50).

Regarding claim 30, the method of claim 28 is discussed above. Anderson et al also teach the steps are repeated a plurality of times (column 20, lines 2).

Regarding claim 31, the method of claim 28 is discussed above. Anderson et al also teach the substrate comprises a surface of a planar support; namely, the support is a flat disc (column 6, lines 49-56).

Regarding claim 32, the method of claim 28 is discussed above. Anderson et al also teach the displacing step causes minimal mixing of deblocking and purging fluids; namely, density differences are used to minimize mixing (column 10, lines 23-24).

Regarding claim 34, the method of claim 28 is discussed above. Anderson et al also teach the substrate comprises a nascent surface of a planar support; namely, the support is a flat disc (column 6, lines 49-56), and the reactions are occurring on the nascent surface created by the previous round of reactions (column 20, lines 2).

Regarding claim 35, the method of claim 28 is discussed above. Anderson et al also teach the purging fluid has a density that is different from the deblocking fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (Column 5, lines 3-38 and Column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (Column 12, lines 28-67 and Fig. 2A-2D).

Regarding claims 36 and 38, the method of claim 28 is discussed above. Anderson et al also teach the deblocking fluid and the purging fluid have a density difference, expressed as the Atwood number, of at least about 0.01. In a single exemplary embodiment, Anderson et al teach the deblocking (detritylation) fluid has a density that is greater than that of methylene chloride (i.e., 1.325 g/mL; column 21, lines 1-10). Detritylation is followed with a wash using acetonitrile as a purging solution, which has a density of 0.714 g/mL (Table II, step 3). Calculating the density difference using pure methyl chloride results in an Atwood number of 0.2996; a higher density deblocking fluid gives a higher Atwood number.

Regarding claim 39, the method of claim 28 is discussed above. Anderson et al also teach the purging fluid is an organic fluid; namely, 50% dichloromethane and 50% dimethylformamide (Table II).

Regarding claim 40, the method of claim 28 is discussed above. Anderson et al also teach the purging fluid comprises an oxidizing agent; namely, the purging fluid is interpreted to be all of the fluids of Table I following the deprotection step i (column 20), which are introduced in one long series of changing densities (column 7, lines 5-19). The series that makes up the purging fluid includes the oxidizing agent iodine (step iv of Table I).

Regarding claims 41 and 42, the method of claim 28 is discussed above. Anderson et al also teach the purging fluid comprises a wash fluid; namely, step 3 of Table II is a washing step using 50% dichloromethane and 50% dimethylformamide (Table II).

Regarding claim 43, the method of claim 41 is discussed above. Anderson et al also teach the wash fluid is acetonitrile (column 13, line 67-column 14, line 1).

Regarding claim 44, the method of claim 28 is discussed above. Anderson et al also teach the deblocking fluid is displaced with a purging fluid in a manner that moves a stratified interface across the surface; namely, interface 124, which is indicative of the stratified layers, is formed during the method (column 12, lines 28-67 and Fig. 2A-2D).

Regarding claim 46, the method of claim 28 is discussed above. Anderson et al also teach the purging fluid limits the efficiency of the deblocking fluid; namely, the deblocking reaction requires acid (e.g., dichloroacetic acid; step i of Table I). Addition of any washing fluid decreases the concentration of acid, thereby limiting the efficiency of deblocking.

Regarding claim 47, the method of claim 29 is discussed above. Anderson et al also teach the hydroxyl groups are 5' OH groups of nucleoside polymers deblocked by the detritylation step (column 19, line 40-column 20, line 50).

Regarding claim 48, the method of claim 28 is discussed above. Anderson et al also teach the step of displacing occurs within a flow cell; namely, an internal space for fluid flow so as to contact a solid support (column 5, lines 20-38).

Regarding claim 50, the method of claim 28 is discussed above. Anderson et al also teach the blocking group is a trityl group (column 19, line 40-column 20, line 50), which is an acid sensitive group, and the deblocking fluid comprises dichloroacetic acid (step i of Table I).

Regarding claim 54, the method of claim 28 is discussed above. Anderson et al also teach the deblocking fluid comprises an organic solvent; namely, acetonitrile (column 13, line 67-column 14, line 1). The vapor pressure of acetonitrile at 0°C and 1 ATM pressure is 24.75 mm Hg, which is 3.3 kPa.

Regarding claim 55, the method of claim 28 is discussed above. Anderson et al also teach contacting the substrate comprising the attached blocked nucleoside polymer with an oxidation fluid prior to contacting with the deblocking fluid; namely, oxidation of an added nucleoside is performed before the sequential addition of the next monomer (Table I, step iv).

Regarding claim 56, Anderson et al teach a method for producing a substrate and at least two oligonucleotides bonded to different locations on a surface of said substrate. In a single exemplary embodiment, Anderson et al teach locations having functional groups in the form of cpg supports having the first monomer attached (column 19, lines 55-58) in accordance with the definition of an addressable array on page 10, lines 13-26 of the specification.

Anderson et al teach contacting tritylated nucleoside monomers with the supports, wherein terminal nucleotides on the supports have been previously detritylated to provide free 5'OH groups (column 19, line 40-column 20, line 50), wherein the 5' OH groups are the functional groups on the surface that bind the blocked (i.e., tritylated) monomers to the locations on the surface. Anderson et al also teach the newly attached nucleosides are subsequently detritylated (column 19, line 40-column 20, line 50), wherein the detritylation fluid is a deblocking fluid (Table I, step i, column 20). Anderson et al further teach washing the surface (Table I, column 20), wherein the reagents are kept separate based on

density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). The washing solution is a purging solution that displaces the deblocking fluid from all of the locations. Anderson et al also teach reacting the newly unblocked monomers at the locations with another blocked nucleoside monomer; namely, the steps of the method are repeated on the substrate to attain the required chain length (column 20, line 2).

While the reference does not use the term "array", the term is defined by the website dictionary.reference.com as "a larger group, number or quantity of people or things".

In addition, while page 6 of the instant specification states that an array "includes any one-dimensional, two-dimensional or substantially two-dimensional (as well as a three-dimensional) arrangement of addressable regions bearing a particular chemical moiety or moieties," the specification yields no limiting definition **requiring** the regions of the array to be addressable.

Anderson et al teach production of a plurality of oligonucleotides attached to cpg substrate ("1. Oligonucleotide Synthesis", columns 19-22 and column 24, lines 5-35). Anderson et al further teaches the method wherein the polymers are cleaved from the support for subsequent use and/or immobilization (column 14 and column 20, liens 10-25); namely, hybridization to oligonucleotides immobilized on solid supports (column 20, lines 20-21). The clearly suggests that the polymers are subsequently immobilized.

Anderson et al does not specifically teach production of an addressable array, or that the oligonucleotides are covalently bonded at the plurality of addressable features.

However, polymer synthesis on cpg supports followed by polymer cleavage for production of an addressable array of covalently attached oligonucleotides was well known and routinely practiced in the art at the time the claimed invention was made as taught by Schleifer (A) and (B).

Schleifer (A) teaches a similar method of polymer synthesis comprising repeated monomer additions to cpg supports (column 9, lines 6-10), cleavage of the polymers from the supports (column 10, lines 10-15) and immobilization of the polymers to feature locations on the array (column 10, lines 37-42)

whereby "costly and time consuming purification step" is avoided while providing a high purity full-length oligonucleotide array (column 10, lines 47-51). Schleifer (A) also teach the full length (is synthesized and cleaved) oligonucleotides are linked to the array via conventional methods of attachment to a substrate (column 10, lines 36-42), wherein the linking agent provides a covalent bond between the oligonucleotide and the substrate surface (column 10, line 65-column 11, line 35). Thus, Schleifer (A) teaches the known technique of covalently linking oligonucleotides to a substrate at a plurality of addressable features (i.e., feature locations).

Schleifer (B) also teaches a similar method of polymer synthesis comprising repeated monomer additions to cpg supports, cleavage of the polymers from the supports and immobilization of the polymers to feature locations on the array (column 9, lines 22-column 10, line 30 and Example 3) whereby an addressable array is produced (see definition of array, column 1, lines 13-15). Schleifer (B) also teaches the deposition of the molecules onto the substrate utilizes covalent coupling of activated oligonucleotides with solid supports (column 9, lines 1-20). Schleifer (B) teaches this polymer synthesis coupled to array production is an efficient, cost-effective method of spatially integrating polymer synthesis and replicate array fabrication (Abstract, column 2, lines 22-31). Thus, Schleifer (B) teaches the known technique of covalently linking oligonucleotides to a substrate at a plurality of addressable features.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the polymers synthesized by Anderson et al to the further step of addressable array fabrication taught by Schleifer (A) and/or (B) to produce an addressable array comprising oligonucleotides covalently bound to the substrate at the plurality of addressable features. One of ordinary skill in the art would have been motivated to do so based on the well known practice of addressable immobilization of pre-synthesized polymers as taught by Schleifer (A) and (B). One of ordinary skill would have been further motivated to do so for the expected benefits of producing replicate arrays via efficient, cost-effective methods of spatially integrating polymer synthesis and array fabrication (Schleifer (B); Abstract, column 2, lines 22-31) and for the further benefits of providing high

purity full-length oligonucleotides while avoiding "costly and time consuming purification step" (Schleifer (A): column 10, lines 47-51).

Alternatively, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the displacement fluid synthesis steps of Anderson et al to the polymer synthesis of either Schleifer (A) or (B). Anderson et al teaches polymer synthesis in particulate beds is problematic in that fluid flow thorough the bed is non-uniform resulting non-uniform reactions and hence inefficient and inaccurate polymer synthesis (columns 1-4). Anderson et al further teach that their method of precise fluid control through the particle bed minimizes the problems of micro and macro-anomalous flow provides precise and efficient polymer synthesis (column 5-6). Therefore, one of ordinary skill in the art would have been motivated to apply the precisely controlled fluid flow of Anderson et al to the particle bed synthesis of Schleifer (A) and/or (B) for the expected benefit of precise and efficient polymer synthesis while eliminating the problems inherent in particle bed synthesis as taught by Anderson (columns 1-6).

In addition, it would have been obvious to the ordinary artisan that the known technique of using the polymer cleavage for production of an addressable array of covalently attached oligonucleotides as taught by Schleifer (A) and (B) could have been applied to the method of Anderson with predictable results because the polymer cleavage for production of an addressable array of covalently attached oligonucleotides as taught by Schleifer (A) and (B) predictably result in production of stable addressable array of oligonucleotides.

Regarding claim 33, the method of claim 56 is discussed above. Anderson et al also teach the substrate comprises a surface of a support containable within a flow cell; namely, internal space for fluid flow so as to contact solid support (column 5, lines 20-38).

Regarding claim 51, the method of claim 33 is discussed above. Anderson et al also teach the substrate is contained within a chamber of flow cell; namely, chamber 24 is which holds the particulate material (i.e., the substrate; figure 1 and column 11, line 24-column 12, lines 27). Chamber 24 is also

connected to upper and lower fluid lines 100 and 102 (Figure 1), which are interpreted as fluid inlet and outlets.

Regarding claim 52, the method of claim 51 is discussed above. Anderson et al also teach the flow cell is oriented an at least partially vertical position; namely, the flow cell is attached to a rotor system, and is spun with the axis vertically (Abstract).

Regarding claim 57, the method of claim 56 is discussed above. Anderson et al also teach the at least two oligonucleotides comprise the same sequence; namely, the solutions are added to the support in a rotor (column 20, lines 55-65), which is interpreted as a single synthesis in a single rotor, producing one full length sequence at more than one location on the support.

Regarding claim 58, the method of claim 56 is discussed above. Anderson et al also teach the at least two oligonucleotides comprise different sequences; namely, at least one location has a failure sequence (column 20, lines 10-25), which is interpreted as a second different sequence in addition to the successfully synthesized sequences.

Regarding claim 59, the method of claim 56 is discussed above. Anderson et al also teach contacting the substrate comprising the bonded blocked nucleoside polymer with an oxidation fluid prior to contacting with the deblocking fluid; namely, oxidation of an added nucleoside is performed before the sequential addition of the next monomer (Table I, step iv).

Regarding claim 61, the method of claim 28 is discussed above. Anderson et al also teach the substrate is planar; namely, the membrane is a flat disk (column 6, lines 49-56).

7. Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993) in view of Schleifer (A) (U.S. Patent No. 6,077,674, issued 20 June 2000) or Schleifer (B) (U.S. Patent No. 6,309,828, issued 30 October 2001) as applied to claim 28 above, and further in view of Greene et al (*Protective Groups in Organic Synthesis*, 3rd ed., Wiley and Sons, New York, 1999, page 106).

Regarding claim 37, the method of claim 28 is discussed above in Section 7.

Neither Anderson et al nor Schleifer (A) or (B) explicitly teach the purging fluid density is higher than the deblocking fluid density.

However, Green et al teach the deblocking (i.e., cleavage) of dimethoxytrityl (i.e., trityl) groups of deoxyribonucleotides using 3% trichloroacetic acid (density 1.62 g/mL) in 95:5 nitromethane/methanol (densities 1.127 and 0.791 g/mL, respectively), with the added advantage that the mixture reduces the levels of depurination of the reaction product (page 106). Depurination results in a degraded product on the array.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not posses characteristic relied on" (205 USPQ 594, second column, first full paragraph). In the instant case, the solvent mixture is predominantly nitromethane, with a density of 1.127 g/mL, with 5% methanol, having a lower density. A final concentration of 3% of the higher density trichloroacetic acid is believed to produce a solution with an overall density nearly equal to that of nitro methane, because similar percentages of both a higher density liquid and a lower density liquid are added. Thus, the final density of the solution of Greene et al is believed to be lower that 1.325 g/mL, which is the density of the purging fluid of Anderson et al. Thus, Greene et al teach the known technique of having a purging fluid density that is higher than the deblocking fluid density.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method as taught by Anderson et al in view of Schleifer (A) or (B) with a deblocking solution of lower density as taught by Greene et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method of producing an addressable

array having the added advantage of having fewer degraded products on the array via a reduction in the levels of depurination of the reaction product as explicitly taught by Greene et al (page 106). In addition, it would have been obvious to the ordinary artisan that the known technique of using the purging fluid density of Greene et al could have been applied to the method of Anderson in view of Schleifer (A) and (B) with predictable results because the purging fluid density of Greene et al predictably results in reliable purging of the array.

8. Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993) in view of Schleifer (A) (U.S. Patent No. 6,077,674, issued 20 June 2000) or Schleifer (B) (U.S. Patent No. 6,309,828, issued 30 October 2001) as applied to claims 28 and 44 above, and further in view of Mian et al (U.S. Patent No. 6,319,469, issued 20 November 2001).

Regarding claim 45, the method of claims 28 and 44 is discussed above in Section 6.

While Anderson et al are silent with respect to specific flow rates, Anderson et al do teach the method wherein the flow rate is controlled and monitored during passage of reagents (column 5,lines 25-27 and column 14, lines 44-53 21). Anderson et al further teach that it is advantageous to control the flow rate because some synthesis steps take more or less time than other steps and because reagent waste resulting from excess use of reagents is expensive (column 21, lines 30-65). Thus, the reference clearly suggests that the flow rate is adjusted to maximize reagents and synthetic step.

In addition, Mian et al teach a method of synthesizing oligonucleotides on a disc (Figure 23b and column 5, lines 65-67), wherein the flow rates are from about 1 cm/sec to about 20 cm/sec having the added advantage that variable flow rates within the claimed range allow fluid transfer over a wide range of times scales as required by the various processes (column 12, lines 40-57). Thus, Mian et al teach the known technique of using the instantly claimed flow rates.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the flow rates of the method of Anderson et al in view of

Schleifer (A) or (B) with the range of flow rates as taught by Mian et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method of producing an addressable array having the added advantage of having flow rates that allow fluid transfer over a wide range of times scales as required by the various processes as explicitly taught by Mian et al (column 12, lines 40-57). In addition, it would have been obvious to the ordinary artisan that the known technique of using the range of flow rates as taught by Mian et al could have been applied to the method of Anderson in view of Schleifer (A) and (B) with predictable results because the range of flow rates as taught by Mian et al predictably results in flow rates suitable for the synthesis of oligonucleotides on an array.

9. Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993) in view of Schleifer (A) (U.S. Patent No. 6,077,674, issued 20 June 2000) or Schleifer (B) (U.S. Patent No. 6,309,828, issued 30 October 2001) as applied to claims 28-29 above, and further in view of Gamble et al (U.S. Patent No. 5,874,554, issued 23 February 1999).

Regarding claim 49, the method of claims 28-29 is discussed above in Section 6.

Neither Anderson et al no Schleifer (A) or (B) teach deposition by pulse-jetting.

However, Gamble et al teach a method of synthesizing oligonucleotides by pulse jetting monomers (Abstract, line 1) with the added benefit that pulse jetting reduces reagent waste (column 1, lines 50-55). Thus, Gamble et al teach the known technique of using pulse-jetting.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method as taught by Anderson et al in view of Schleifer (A) of (B) with the pulse jetting of monomers as taught by Gamble et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted a method of producing an addressable array having the added advantage of reduced reagent waste as explicitly taught by Gamble et al (column 1, lines 50-55). In

addition, it would have been obvious to the ordinary artisan that the known technique of using the pulse jetting of monomers as taught by Gamble et al could have been applied to the method of Anderson in view of Schleifer (A) and (B) with predictable results because the pulse jetting of monomers as taught by Gamble et al predictably results in a reliable method of depositing solutions on an array.

10. Claim 53 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993) in view of Schleifer (A) (U.S. Patent No. 6,077,674, issued 20 June 2000) or Schleifer (B) (U.S. Patent No. 6,309,828, issued 30 October 2001) as applied to claims 28 and 44 above, and further in view of Farr (U.S. Patent No. 3,969,250, issued 13 July 1976).

Regarding claim 53, the method of claims 28 and 44 is discussed above in Section 6.

Neither Anderson et al nor Schleifer (A) or (B) teach a pressure gradient.

However, Farr teaches stratification of liquids using a pressure gradient; namely, creation of supernatant fluid by centrifuging immiscible liquids (column 1, lines 5-10) with the added advantage that the stratification (i.e., the creation of a supernatant) eliminates the need for decanting, thereby minimizing labor and possible contamination of the sample (column 2, lines 24-26). Thus, Farr teaches the known technique of using a pressure gradient.

It would therefore have been obvious to a person or ordinary skill in the art at the time the claimed invention was made to have modified the method comprising a stratified interface as taught by Anderson et al in view of Schleifer (A) or (B) by using a pressure gradient as taught by Farr with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method of producing an addressable array having the added advantage of minimizing labor and possible contamination of the sample as explicitly taught by Farr (column 2, lines 24-26). In addition, it would have been obvious to the ordinary artisan that the known technique of using the pressure gradient of Farr could have been applied to the

method of Anderson in view of Schleifer (A) and (B) with predictable results because the pressure gradient of Farr predictably results in reliable method of stratifying fluids.

Response to Arguments

11. Applicant's arguments filed 2 November 2007 (i.e., the "Remarks") have been fully considered but they are not persuasive for the reason(s) listed below.

A. Applicant argues on page 7 of the Remarks that the claims are no in condition for allowance.

However, as detailed in the rejections above, Applicant's amendment to require the covalent bonding of the oligonucleotides to the substrate was well known in the art at the time the claimed invention was made. Thus, the obviousness rejections are maintained.

B. Applicant further argues on page 7 of the Remarks that claim 28 has been amended to specify the produce array comprises "said" substrate that is first mentioned in step (a) of the claim.

However, Applicant's assertion is not necessarily true. Line 2 of claim 28 recites "oligonucleotides on a substrate" and line 3 of claim 28 contains a second recitation of "a substrate." Because the second recitation in line 3 of claim 28 is not "the" or "said" substrate, the second recitation encompasses an **additional** substrate that is **distinct** from the substrate of line 2 of claim 28. Therefore, "said substrate" of the last line of claim 28 can refer to **either** of the two substrates. Thus, the claim is broadly interpreted such that "said substrate" of the last line of claim 28 is merely the final substrate produced by the method, which is the recited "a substrate" of line 2 of the claim.

Further, page 19 of the instant specification state that "[i]n the specification and the appended claims, the singular forms "a," "an" and "the" include plural reference unless the context clearly dictates otherwise." Thus, the claim is interpreted as referring to a plurality of substrates, and the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding

"a substrate" (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]).

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571) 272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Robert T. Crow
Examiner
Art Unit 1634

DIANA JOHANNSEN
PRIMARY EXAMINER